General

Guideline Title

ACR Appropriateness Criteria® non-spine bone metastases.

Bibliographic Source(s)

Kim EY, Chapman TR, Ryu S, Chang EL, Galanopoulos N, Jones J, Kubicky CD, Lee CP, Teh BS, Traughber BJ, Van Poznak C, Vassil AD, Weber K, Shek-Man Lo S, Expert Panel on Radiation Oncologyâ€“Bone Metastases. ACR Appropriateness CriteriaÂ® non-spine bone metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 11 p. [33 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lutz ST, Shek-Man Lo S, Howell DD, Chang EL, Galanopoulos N, Kim EY, Konski AA, Pandit-Taskar ND, Ryu S, Silverman LN, Van Poznak C, Weber K, Expert Panel on Radiation Oncology-Bone Metastases. ACR Appropriateness Criteria® non-spine bone metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 9 p. [23 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Non-Spine Bone Metastases

Variant 1: 52-year-old man with a history of a T1N0M0 non–small-cell lung cancer. Two years after lobectomy, he is found to have a painful metastasis in the right femoral neck. The lesion is 3.5 cm in size with greater than 50% erosion of the medial bone cortex. Karnofsky performance status (KPS) 90. No other metastatic disease is found. He has had no previous therapy other than lobectomy.

Treatment	Rating	Comments
Surgical intervention followed by EBRT, then systemic therapy	9	
Surgical intervention followed by systemic therapy alone	5	

Treatment	Rating	Comments
EBRT alone	3	This treatment is associated with a high risk of pathologic fracture without prophylactic internal fixation, as evaluated by certain criteria.
EBRT followed by systemic therapy	3	This treatment is associated with a high risk of pathologic fracture without prophylactic internal fixation, as evaluated by certain criteria.
Surgical intervention alone	3	
Hospice after treatment of the femur	2	
Systemic therapy alone (may include biologic agents, bisphosphonates, and/or chemotherapy)	2	
Observation	1	
Direct hospice placement	1	
Radiation Therapy Dose		
8 Gy/1 fraction	4	
20 Gy/5 fractions	5	
24 Gy/6 fractions	6	A high biologically effective dose of radiation may be beneficial for this patient with an excellent KPS and oligometastatic disease.
30 Gy/10 fractions	8	
35 Gy/14 fractions	4	
40 Gy/20 fractions	4	
Treatment Technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
AP/PA	8	
3-D CRT	8	
IMRT	3	
SBRT	2	
Proton therapy to the bone metastasis	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: 62-year-old woman with estrogen receptor positive/progesterone receptor positive breast cancer, HER2-neu nonamplified. She develops a painful lytic bone metastasis in humerus after 4 years of a single-line of adjuvant hormonal therapy. There is minimal invasion of bone cortex, and the lesion is thought to have a low fracture risk per orthopedic surgery consult. KPS is 90. Bone scan demonstrates a few other asymptomatic bone metastases.

Treatment	Rating	Comments
EBRT followed by systemic therapy	8	
Systemic therapy alone (may include biologic agents, bisphosphonates, and/or chemotherapy)	4	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment	Rating	Comments
bisphosphonates or RANK ligand inhibitor)		
EBRT alone	3	
Radiopharmaceuticals	2	
Surgical intervention	2	
Direct hospice placement	1	
Hospice after treatment of the humerus	1	
Radiation Therapy Dose		
8 Gy/1 fraction	8	
20 Gy/5 fractions	8	
24 Gy/6 fractions	8	
30 Gy/10 fractions	8	
35 Gy/14 fractions	5	
40 Gy/20 fractions	3	
Treatment Technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
AP/PA	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: 65-year-old woman with metastatic hormone-receptor positive breast cancer currently on hormonal and bisphosphonate therapy for skeletal-dominant metastatic disease. She received palliative radiation (30 Gy/10 fractions) to a painful lesion in the right humerus 3 years ago with good pain relief but now has recurrent pain at this site. Radiographs show a lytic lesion with no radiographic evidence of impending fracture. She has several other asymptomatic skeletal lesions and a new 1.5-cm lung metastasis.

Treatment	Rating	Comments
EBRT reirradiation to symptomatic lesion	8	
Consider changes to systemic therapy only	5	
Radiopharmaceuticals	3	
Surgical intervention	3	
Direct hospice placement	2	
Hospice after treatment of the humerus	2	
Radiation Therapy Dose		
8 Gy/1 fraction	8	

Treatment	Rating	Comments
20 Gy/5 fractions	8	
24 Gy/6 fractions	8	
30 Gy/10 fractions	7	
35 Gy/14 fractions	5	
40 Gy/20 fractions	3	
Treatment Technique		
Clinical simulation	5	
3-D CRT	8	
Fluoroscopic simulation or 2-D RT	8	
CT simulation	9	
AP/PA	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field

Variant 4: 66-year-old man with metastatic hormone-refractory prostate cancer. He has widespread osteoblastic skeletal disease with increasingly painful lesions in the lumbar spine, hips, and extremities. Prior therapy has included hormonal therapy, bisphosphonates, docetaxel chemotherapy, and EBRT to one of his painful hip lesions.

Treatment	Rating	Comments
Radiopharmaceuticals and EBRT to symptomatic lesions	8	
Radiopharmaceuticals	8	
EBRT to most symptomatic lesions	7	EBRT is an effective modality for pain relief of selected lesions, but the amount of bone marrow treated should be minimized to prevent compromising the patient's remaining systemic therapy options.
Direct hospice placement	5	
Consider changes to systemic therapy only	4	
Medical pain management only	4	
Radiation Therapy Dose (If EBRT used)		
8 Gy/1 fraction	8	
20 Gy/5 fractions	7	
24 Gy/6 fractions	7	
30 Gy/10 fractions	7	
35 Gy/14 fractions	4	
40 Gy/20 fractions	3	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Treatment Technique (If EBRT used) Treatment	Rating	Comments
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: 47-year-old man with a history of malignant melanoma, now with a painful metastatic lesion in the left scapula. KPS is 70. He has had no prior therapy for metastatic disease. Staging scans show an asymptomatic 3-cm liver metastasis.

Treatment	Rating	Comments
EBRT and consideration of systemic therapy	8	
Systemic therapy alone	4	This patient may be a candidate for targeted therapies, but radiation offers rapid palliation of pain.
EBRT alone	3	
Hospice after treatment of the scapula metastasis	2	
Direct hospice placement	2	
Radiopharmaceuticals	2	
Radiation Therapy Dose		
8 Gy/1 fraction	8	
20 Gy/5 fractions	7	
24 Gy/6 fractions	8	
30 Gy/10 fractions	8	
35 Gy/14 fractions	6	
40 Gy/20 fractions	3	
Treatment Technique		
Clinical simulation	5	
Fluoroscopic simulation or 2-D RT	7	
CT simulation	8	
3-D CRT	8	
IMRT	2	
SBRT	2	
Proton therapy to the bone metastasis	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

Bone is a common sites of metastasis, affecting patients with a wide variety of malignancies including breast, prostate, lung, colorectal, bladder, endometrial, thyroid, kidney, myeloma, and melanoma. The presence of tumor in bone can cause significant morbidity including pain, neurologic dysfunction, hypercalcemia, and pathologic fracture leading to significant functional loss. The optimal treatment of a patient with bone metastases depends on many factors, including evaluation of the patient's goals of care, performance status, mechanical stability of the affected bone, life expectancy, and overall extent of disease. Both osteolytic and osteoblastic lesions may be associated with pain and risk of fracture. Management decisions frequently involve collaboration among several types of specialists, including diagnostic radiologists, radiation oncologists, medical oncologists, surgeons, pain medicine specialists, physiatrists, and palliative care professionals. Similar to the approaches used for patients treated with curative intent, optimal management of patients with bone metastases requires multidisciplinary consideration of localized therapies such as surgery and external beam radiation therapy (EBRT) with systemic therapies including pain medications, chemotherapy, hormonal therapy (HT), osteoclast inhibitors (OI), and radiopharmaceuticals.

Oftentimes, patients who present with multifocal bone metastases are treated first with medical therapies including narcotics, chemotherapy, HT, bisphosphonates, radiopharmaceuticals, and receptor activator of NF-kB (RANK) ligand inhibitors. EBRT is usually reserved for when a specific metastatic lesion causes significant local symptoms such as pain or creates a risk for pathological fracture or neurologic injury. Surgical stabilization can treat or prevent the morbidity of a pathologic fracture, particularly in weight-bearing bones. In addition, the alpha-emitting radiopharmaceutical therapy, radium 223 dichloride, has a place in the management of patients with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease.

Variant 1: 52-year-old man with a history of a T1N0M0 non-small-cell lung cancer. Two years after lobectomy, he is found to have a painful metastasis in the right femoral neck. The lesion is 3.5 cm in size with greater than 50% erosion of the medial bone cortex. Karnofsky performance status (KPS) 90. No other metastatic disease is found. He has had no previous therapy other than lobectomy.

This patient has newly diagnosed metastatic disease at a single site (femur), an excellent performance status, and has not previously received systemic therapy. Systemic therapy (including biologic agents, chemotherapy, and OI) will be critical for systemic disease control. However, he is at elevated risk of developing pathologic fracture in the near future and would benefit from immediate attention to the femoral lesion.

The most useful means of predicting the risk for pathologic fracture includes evaluation by a published scoring system based on anatomic site, degree of pain, type of lesion (blastic, mixed, lytic), and tumor size. Another simplified method of predicting pathologic fracture in the femur describes an elevated risk in lesions with >3 cm cortical involvement.

This patient should be evaluated by an orthopedic surgeon for consideration of surgical stabilization of the femur. If he undergoes surgical stabilization, postoperative radiotherapy should be considered. If he does not undergo surgical stabilization, then immediate radiotherapy is indicated. The goals of therapy would be to control pain as well as preserve ambulatory function.

Radiation can be delivered to this site most efficiently through parallel opposed anterior and posterior fields. A strip of skin and soft tissue, as large as possible, should be spared to reduce the risk of long-term lower-extremity lymphedema, which can be associated with full-circumference extremity radiation.

This patient also has oligometastatic disease. The optimal management of oligometastases is an active area of research. Investigations comparing site-specific localized therapy to a more systemic approach with or without localized therapy are ongoing. Some have argued that patients with minimal sites of bone-only metastatic disease (deemed "oligometastatic") from certain disease may be treated with curative intent, though the data to confirm that stance are still to be accrued.

Single fraction radiotherapy (8 Gy × 1), when compared to higher-dose multifraction regimens, has been associated with a higher risk of postradiation pathologic fracture in femoral metastases. If this patient does not undergo surgical stabilization, then a higher-dose multifraction regimen would be reasonable. Local therapy should be followed by systemic therapy including consideration of OI. In light of the slight risk of jaw osteonecrosis associated with OI administration, a pretreatment dental evaluation to assess dentition and potential risk prior to OI use might be warranted (see Variant 1 above).

Variant 2: 62-year-old woman with estrogen-receptor positive/progesterone-receptor positive breast cancer, HER2/neu nonamplified. She develops a painful lytic bone metastasis in the right humerus after 4 years of a single-line of adjuvant hormonal therapy. There is minimal invasion of bone cortex, and the lesion is thought to have a low fracture risk per orthopedic surgery consult. KPS is 90. Bone scan demonstrates a few other asymptomatic bone metastases.

This patient has a good performance status and multiple sites of metastatic disease, but has a symptomatic lesion in a non-weight-bearing bone. This patient has a life expectancy that may be measured in years. This patient (as all patients) should receive appropriate analgesic therapy as a first-line treatment to provide rapid relief.

In general, the setup and prescription points for treatment should follow those outlined by the International Consensus on Palliative Radiotherapy Endpoints for future clinical trials, which were updated recently. Fluoroscopic simulation, computed tomography (CT) simulation, and clinical simulation are all acceptable methods for planning radiation fields. There are no data to suggest that highly conformal therapy with intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), proton therapy, or brachytherapy would improve the outcome for this patient.

EBRT provides at least partial pain relief in 50% to 80% of patients, and most series suggest a rate of complete pain relief in about one-third of patients. Although a recent international survey showed 101 different dose schedules in common use for treating painful bone metastases with EBRT, the rates of pain relief are equivalent for fractionation schemes including 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, and a single 8 Gy fraction. Single-fraction treatment optimizes patient convenience and reduces acute side effects but is associated with an approximate 20% rate of retreatment to the same site compared to an 8% retreatment rate with the more prolonged courses.

Due to the presence of multifocal disease, systemic chemotherapy options should be explored, and current practice patterns also should include consideration of the use of OI. If both palliative radiotherapy and palliative systemic chemotherapy are to be delivered to this patient, they should be given sequentially rather than concurrently. OI have the ability to decrease the risk of skeletal-related events (fracture, need for surgery or radiation to bone, spinal cord compression, and hypercalcemia of malignancy) as well as the ability to decrease pain from bone metastases and improve quality of life in patients with certain disease histologies. OI therapy is an adjunctive therapy to radiation. In addition, it may alleviate metastatic bone pain and is routinely administered indefinitely. Inhibiting osteoclast activity does not appear to impart a survival advantage. Recognized effects of the toxicities of potent OI include renal dysfunction (with intravenous bisphosphonates), hypocalcemia, and osteonecrosis of the jaw (see Variant 2 above).

Variant 3: 65-year-old woman with metastatic hormone-receptor positive breast cancer currently on hormonal and bisphosphonate therapy for skeletal-dominant metastatic disease. She received palliative radiation (30 Gy/10 fractions) to a painful lesion in the right humerus 3 years ago with good pain relief but now has recurrent pain at this site. Radiographs show a lytic lesion with no radiographic evidence of impending fracture. She has several other asymptomatic skeletal lesions and a new 1.5-cm lung metastasis.

This patient has pain at a site that has been previously irradiated. She had initial pain relief with treatment. Available data from multiple smaller, retrospective studies suggest that retreatment with EBRT may provide a reasonable chance of pain relief in 33% to 84% of patients. A recent meta-analysis of 10 studies, including data from 2,694 patients, estimated pain response in 58% of patients who received reirradiation for painful bone metastases. A recently completed international randomized prospective phase III trial compared a single-fraction (8 Gy x 1) reirradiation schedule to a multiple-fraction regimen (20 Gy in 5 to 8 fractions) in 850 patients with previously irradiated bone metastases. The majority of patients had prostate, breast, or lung cancers. The single-fraction regimen was not inferior to the multiple-fraction regimen with respect to pain control assessment at 2 months. Acute toxicities were worse in the multiple-fraction arm.

As in any case of reirradiation, care should be taken to avoid combined doses greater than the normal tissue tolerances of structures within the retreated volumes. The recurrence of pain in any long bone necessitates a reassessment of pathologic fracture risk before delivering reirradiation. Treatment should be planned to spare a skin and soft-tissue strip to minimize the risk of developing late chronic upper extremity lymphedema. Fluoroscopic simulation, CT simulation, and clinical simulation are all acceptable methods for planning radiation fields. There are no data to suggest that highly conformal therapy with IMRT, SBRT, brachytherapy, or proton therapy would improve the outcome for this patient.

Systemic chemotherapy can be considered depending on the patient's previous exposure to chemotherapy and her tolerance of further therapy. This patient's disease has progressed on bisphosphonates, and receptor activator of NF-kB (RANK) ligand inhibitors may be of use. If cytotoxic therapy is considered, it should be delivered sequentially with palliative radiotherapy rather than concurrently. Duration of radiation therapy should be weighed against the urgency of initiating a new line of systemic therapy. A shorter course of palliative reirradiation would potentially delay chemotherapy less than a longer treatment course.

The American Society of Clinical Oncology Guidelines for the use of bone modifying agents in metastatic breast cancer recommend the use of OI, bisphosphonate or denosumab, be continued until there is evidence of substantial decline in the patient's clinical status. These drugs may reduce the risk of subsequent skeletal-related events and may aid in controlling bone pain. It is of note that in the pooled analysis of the phase III studies of denosumab versus zoledronic acid, denosumab demonstrated superiority in delaying the time to subsequent skeletal-related events with a relative risk of 0.82 (95% confidence interval [CI], 0.75 to 0.90) $P<0.001$ (see Variant 3 above).

Variant 4: 66-year-old man with metastatic hormone-refractory prostate cancer. He has widespread osteoblastic skeletal disease with increasingly painful lesions in the lumbar spine, hips, and extremities. Prior therapy has included hormonal therapy, bisphosphonates,

docetaxel chemotherapy, and EBRT to one of his painful hip lesions.

This patient has been heavily pretreated for metastatic prostate cancer and now has hormone-refractory disease. The patient may consider additional systemic therapy. As his bone metastases appear relatively symptomatic, Sipuleucel-T is not a likely next step. Abiraterone/prednisone and enzalutamide may be considered options if not used already. Note that enzalutamide is U.S. Food and Drug Administration (FDA) approved for disease progression after docetaxel therapy. In addition, a clinical trial, cabozantinib, or mitoxantrone may be options for this individual depending on his goals of care, marrow reserve, and performance status.

Although it may be technically possible to deliver EBRT to multiple symptomatic lesions, his burden of disease suggests he may be a favorable candidate for radiopharmaceutical therapy. Multiple series have reported pain responses rates ranging from 45% to 80% with samarium-153 or strontium-89. An international prospective randomized trial of radium-223 versus placebo showed improvements in quality of life scores, decreased skeletal events, and improved overall survival with administration of radium-223.

The use of radiopharmaceuticals does not preclude the delivery of palliative EBRT. If this patient were to receive focused EBRT to painful lesions, it would be prudent to consider the volume of bone marrow within the treatment field given the potential for diffuse bone marrow suppression that has previously been reported with radiopharmaceuticals (see Variant 4 above.)

Variant 5: 47-year-old man with a history of malignant melanoma, now with a painful metastatic lesion in the left scapula. KPS is 70. He has had no prior therapy for metastatic disease. Staging scans show an asymptomatic 3-cm liver metastasis.

This patient has severe pain from a single site of bone metastases with a functional performance status. This patient (as with all patients) should receive appropriate analgesic therapy as first-line treatment to provide rapid symptom relief. Systemic therapy for melanoma is an evolving field, but overall prognosis remains poor. Melanoma is traditionally considered less sensitive to conventionally fractionated radiotherapy. The majority of studies evaluating radiotherapy for skeletal metastases consist of prostate, breast, and lung cancer patients. There is inadequate data available to determine whether tumor histologies traditionally thought of as "radioresistant" respond equally well to palliative radiotherapy as other more traditionally "radiosensitive" histologies. The ability of melanoma cell lines to repair sublethal DNA damage suggests melanoma may be more sensitive to large doses per fraction or a hypofractionated course of therapy.

Skin and soft-tissue sparing techniques should be utilized. A single treatment would minimize his time commitment, transportation requirements, and discomfort from being transferred on and off the treatment table. Fluoroscopic simulation, CT simulation, and clinical simulation are all acceptable methods for planning radiation fields. Treatment with large fractions might be more likely to cause a temporary pain flare, but anti-inflammatory medications are capable of minimizing this effect. There are no data to suggest that highly conformal therapy with IMRT, SBRT, brachytherapy, or proton therapy would improve the outcome for this patient (see Variant 5 above).

Summary of Recommendations

- EBRT successfully provides rapid palliative relief from painful bone metastases in most cases.
- The acute side effects of palliative EBRT are usually minimal and self-limiting, whereas long-term side effects are uncommon and may not be clinically relevant in a patient group with limited life expectancy.
- Radiotherapy is not commonly recommended for asymptomatic bone metastases that are not associated with a risk of pathologic fracture as the primary goals of therapy are pain relief and functional preservation.
- Prospective randomized trials have proven equivalent pain relief with varied fractionation schemes, including 8 Gy in one fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, or 30 Gy in 10 fractions. Prolonged courses are associated with a lower incidence of retreatment, while shorter courses maximize patient and caregiver convenience by reducing the number of trips to the radiation department.
- Patients who undergo surgical stabilization for impending or completed pathologic fracture of a long bone may be treated with postoperative radiotherapy to 30 Gy in 10 fractions, 24 Gy in 6 fractions, 20 Gy in 5 fractions, or 8 Gy in a single fraction.
- Reirradiation with EBRT may be feasible and effective, though retreatment to sites including radiation-sensitive critical structures should include careful consideration of the cumulative radiation doses that may exceed normal tissue tolerance. Reirradiation with a single 8 Gy fraction is not inferior to multiple-fraction radiation and has less acute toxicity.
- Management of metastatic bone disease is palliative. A multidisciplinary team of care providers, including the palliative care team, should be available to the patient. Goals of care should be defined with the patient. Hospice referral should be considered if the life expectancy is 6 months or less, but this does not preclude the use of radiation for pain control.

Abbreviations

- AP/PA, anterior-posterior/posterior-anterior
- 2-D RT, 2-dimensional radiation therapy
- 3-D CRT, 3-dimensional conformal radiation therapy

- CT, computed tomography
- EBRT, external beam radiation therapy
- HER2, human epidermal growth factor receptor 2
- IMRT, intensity-modulated radiation therapy
- KPS, Karnofsky performance status
- RANK, receptor activator of NF-kB
- SBRT, stereotactic body radiation therapy

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Non-spine bone metastases with cancer (e.g., breast, lung, colorectal or prostate cancer)

Guideline Category

Risk Assessment

Treatment

Clinical Specialty

Oncology

Radiation Oncology

Radiology

Intended Users

Health Plans

Hospitals

Managed Care Organizations

Physicians

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of various radiologic procedures for the treatment of patients with non-spine bone metastases

Target Population

Patients with non-spine bone metastases

Interventions and Practices Considered

1. External beam radiation therapy (EBRT)
    - EBRT alone
    - Followed by systematic therapy
    - With radiopharmaceuticals to symptomatic lesions
    - EBRT reirradiation to symptomatic lesion
    - EBRT to most symptomatic lesions
2. Radiopharmaceuticals
3. Surgical intervention
    - Surgical intervention alone
    - Followed by systemic therapy alone
    - Followed by EBRT, then systemic therapy
4. Hospice placement (direct or after treatment)
5. Systemic therapy alone (may include biologic agents, bisphosphonates, receptor activator of NF-kB [RANK] ligand inhibitors, and/or chemotherapy)
6. Consideration of changes to systemic therapy
7. Medical pain management only
8. Observation
9. Consideration of radiation therapy doses
10. Treatment techniques
    - Clinical simulation
    - Fluoroscopic simulation or 2-dimensional radiation therapy (2-D RT)
    - Computed tomography (CT) simulation
    - Anterior-posterior/posterior-anterior (AP/PA)
    - 3-dimensional conformal radiation therapy (3-D CRT)
    - Intensity-modulated radiation therapy (IMRT)
    - Stereotactic body radiation therapy (SBRT)
    - Proton therapy to the bone metastasis

Major Outcomes Considered

- Quality of life
- Pain relief
- Functional status
- Local tumor control
- Risk of pathologic fracture
- Survival
- Side effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Summary

Of the 23 citations in the original bibliography, 14 citations were retained in the final document. Articles were removed from the original bibliography if they were more than 10 years old and did not contribute to the evidence or they were no longer cited in the revised narrative text.

A new literature search was conducted in July 2013 to identify additional evidence published since the *ACR Appropriateness Criteria® Non-Spine Bone Metastases* topic was finalized. Using the search strategy described in the literature search companion (see the "Availability of Companion Documents" field), 94 articles were found. No articles were added to the bibliography due to either poor study design, the articles were not relevant or generalizable to the topic, the results were unclear, misinterpreted, or biased, or the articles were already cited in the original bibliography.

The author added 19 citations from bibliographies, Web sites, or books, not found in the new literature search.

See also the American College of Radiology (ACR) Appropriateness Criteria® literature search process document (see the "Availability of Companion Documents" field) for further information.

Number of Source Documents

Of the 23 citations in the original bibliography, 14 citations were retained in the final document. The new literature search conducted in July 2013 identified no new articles. The author added 19 citations from bibliographies, Web sites, or books, not found in the new literature search.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Study Quality Category Definitions

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - There are important study design limitations.

Category 4 - The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

a. The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description).
b. The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence.
c. The study is an expert opinion or consensus document.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development documents (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness. When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the second rating round, the recommendation is "may be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized and economical process. For additional information on the ratings process see the Rating Round Information document on the ACR Web site.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current literature and expert panel consensus.

Summary of Evidence

Of the 33 references cited in the *ACR Appropriateness Criteria® Non-Spine Bone Metastases* document, all of them are categorized as therapeutic references including 10 well-designed studies. There are 23 references that may not be useful as primary evidence.

While there are references that report on studies with design limitations, 10 well-designed studies provide good evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Selection of appropriate radiologic treatments for patients with non-spine bone metastases

Potential Harms

- Recognized effects of the toxicities of potent osteoclast inhibitors (OI) include renal dysfunction (with intravenous bisphosphonates), hypocalcemia, and osteonecrosis of the jaw. In light of the slight risk of jaw osteonecrosis associated with OI administration, a pretreatment dental evaluation to assess dentition and potential risk prior to OI use might be warranted.
- External beam radiation therapy (EBRT) is associated with a high risk of pathologic fracture without prophylactic internal fixation, as evaluated by certain criteria.
- The acute side effects of palliative EBRT are usually minimal and self-limiting, whereas long-term side effects are uncommon and may not be clinically relevant in a patient group with limited life expectancy.
- Single fraction raditherapy (8 Gy × 1), when compared to higher-dose multifraction regimens, has been associated with a higher risk of postradiation pathologic fracture in femoral metastases.
- Single-fraction treatment optimizes patient convenience and reduces acute side effects but is associated with about a 20% rate of retreatment to the same site compared to an 8% retreatment rate with the more prolonged courses.
- A recently completed international randomized prospective phase III trial compared a single-fraction (8 Gy × 1) reirradiation schedule to a multiple-fraction regimen (20 Gy in 5 to 8 fractions) in 850 patients with previously irradiated bone metastases. The majority of patients had prostate, breast, or lung cancers. The single-fraction regimen was not inferior to the multiple-fraction regimen with respect to pain control assessment at 2 months. Acute toxicities were worse in the multiple-fraction arm.
- Treatment with large fractions might be more likely to cause a temporary pain flare, but anti-inflammatory medications are capable of minimizing this effect.
- Retreatment to sites including radiation-sensitive critical structures should include careful consideration of the cumulative radiation doses that may exceed normal tissue tolerance. Reirradiation with a single 8 Gy fraction is not inferior to multiple-fraction radiation and has less acute toxicity.
- Treatment should be planned to spare a skin and soft-tissue strip to minimize the risk of developing late chronic upper extremity lymphedema.
- Radiopharmaceuticals have a potential for diffuse bone marrow suppression.

Qualifying Statements

Qualifying Statements

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

End of Life Care

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Kim EY, Chapman TR, Ryu S, Chang EL, Galanopoulos N, Jones J, Kubicky CD, Lee CP, Teh BS, Traughber BJ, Van Poznak C, Vassil AD, Weber K, Shek-Man Lo S, Expert Panel on Radiation Oncologyâ€“Bone Metastases. ACR Appropriateness CriteriaÂ® non-spine bone metastases [online publication]. Reston (VA): American College of Radiology (ACR); 2014. 11 p. [33 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

1996 (revised 2014)

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Bone Metastases

Composition of Group That Authored the Guideline

Panel Members: Edward Y. Kim, MD (*Principal Author*); Tobias R. Chapman, MD (*Research Author*); Samuel Ryu, MD (*Panel Vice-chair*); Eric L. Chang, MD; Nicholas Galanopoulos, MD; Joshua Jones, MD; Charlotte D. Kubicky, MD, PhD; Charles P. Lee, MD; Bin S. Teh, MD; Bryan J. Traughber, MD; Catherine Van Poznak, MD; Andrew D. Vassil, MD; Kristy Weber, MD; Simon Shek-Man Lo, MB, ChB (*Panel Chair*)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Lutz ST, Shek-Man Lo S, Howell DD, Chang EL, Galanopoulos N, Kim EY, Konski AA, Pandit-Taskar ND, Ryu S, Silverman LN, Van Poznak C, Weber K, Expert Panel on Radiation Oncology-Bone Metastases. ACR Appropriateness Criteria® non-spine bone metastases. [online publication]. Reston (VA): American College of Radiology (ACR); 2011. 9 p. [23 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available from the American College of Radiology (ACR) Web site .

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Feb. 3 p. Electronic copies: Available from the American College of Radiology (ACR) Web site .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Electronic copies: Available from the ACR Web site .

- ACR Appropriateness Criteria®. Evidence table development – therapeutic studies. Reston (VA): American College of Radiology; 2013 Nov. 4 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria® non-spine bone metastases. Evidence table. Reston (VA): American College of Radiology; 2014. 19 p. Electronic copies: Available from the ACR Web site .
- ACR Appropriateness Criteria® non-spine bone metastases. Literature search. Reston (VA): American College of Radiology; 2014. 1 p. Electronic copies: Available from the ACR Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on March 25, 1999. The information was verified by the guideline developer on September 9, 1999. The summary was updated on February 12, 2002. The information was verified again by the guideline developer on March 25, 2002. This summary was updated by ECRI most recently on November 12, 2004. The information was verified by the guideline developer on December 21, 2004. This summary was updated by ECRI Institute on August 13, 2009. This summary was updated by ECRI Institute on March 20, 2012. This summary was updated by ECRI Institute on August 3, 2015.

Copyright Statement

Disclaimer

NGC Disclaimer